IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants:	Richard P. Batycky, Giovanni Caponetti, Mariko Childs, Elliot Ehrich, Karen Fu, Jeffrey S. Hrkach, Wen-I Li, Michael M. Lipp, Mei-Ling Pan and Jason Summa		
Application No:	10/607,571	Group No:	1616
Filed:	June 26, 2003	Examiner:	J. H. Alstrum Acevedo
Confirmation No.:	6287		
Title:	INHALABLE EPINEPHRINE		

APPEAL BRIEF

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Brief is being filed pursuant to 37 CFR 41.37. The fee under 37 CFR 41.20(b)(2) of $500 was paid on November 9, 2006. The difference between the fee paid on November 9, 2006 and the fee currently due under 41.20(b)(2) ($540) is paid herewith. The required sections under 37 CFR 41.37 are set forth below under separate headings.

(1) The Real Party of Interest

The real part of interest in this appeal is Alkermes, Inc., by virtue of the Assignment recorded on June 2, 2009 at Reel 022764 and Frames 0088-0103.

(2) Related Appeals and Interferences

There are no related appeals or interferences at this time known to the appellant, the assignee or its representative which will directly affect or be directly affected by or have a bearing in the Board's decision in the pending appeal.

(3) Status of the Claims

Claims 140-143, 146-150, 153 and 156-173 are pending and are said to be finally rejected (See Office Action Summary). **Claims 140-143, 146-150, 153 and 156-173 are appealed**. Claims 1-139, 144-145, 151, 152, 154 and 155 have been canceled. Claim 171 (which is not listed in any specific rejection) is also said to be subjected to an objection, being allowable but dependent on a rejected base claim. Thus, its inclusion in the list of claims as rejected on the Summary appears to be an error. However, out of an abundance of caution, if this claim is also rejected that rejection is also appealed[1]. No claims are withdrawn from consideration.

(4) Status of the Amendments

No claim amendments after Final Rejection were filed.

(5) Summary of Claimed Subject Matter

Appealed claim 140 is directed to a method of administering spray-dried particles of epinephrine and a pharmaceutically acceptable excipient to the respiratory system of a patient via inhalation wherein the particles comprise at least about 50 micrograms of epinephrine and are administered in a single inhalation and wherein the particles have a tap density of less than 0.4 g/cm^3 and posses a fine particle fraction of less than 5.6 microns of at least 45%. Support for the claim is found on page 4, lines 18-25; page 6, line 29 to page 7, line 4 (spray dried particles); page 31, lines 8-15 (low tap density); page 56, lines 2-7 (dose).

Claims 142-143, 146-150, 153 and 156-171 depend either directly or indirectly from claim 140. Claims 142-144 recite percent the presence of 95%, 45% and 30% by

[1] It is believed that an inclusion of claim 171 in any rejection at this stage will necessitate reopening prosecution in any event.

weight of epinephrine or its salt respectively. Support for claims 142-144 is found on page 13, lines 1-15. Claims 146-150 recite that epinephrine is present in amorphous or crystalline form or that the pharmaceutically acceptable excipient is in amorphous or crystalline form. Support for claims 146-150 is found on page 37, lines 24-31. Claim 153 recites that the particles comprise about 250 micrograms to about 5 milligrams of epinephrine. Support for claim 153 is found on page 56, lines 6-7. Claims 156-158 recite that the particles are administered to the upper airways or alveoli region of the lungs. Support for claims 156-158 is found on page 45, lines 20-31. Claims 159 and 160 recite that epinephrine released from the particles acts systemically or locally respectively. Support for claims 159 and 160 is found on page 46, lines 10-15. Claims 161 and 162 recite that the patient is suffering from anaphylaxis or a condition selected from bronchoconstriction, bronchospasm, airway constriction and edema. Support for claims 161 and 162 is found on page 43, lines 25-30. Claim 163 recites that the Cmax of the present method is lower than for a non-intravenous injection for the same dose of epinephrine. Claims 164 depends from claim 163 and recites that various routes of non-intravenous injection. Support for claims 163 and 164 is found on page 26, lines 27-33. Claims 165-166 recite that the Tmax of the present method is lower than the T-max of a non-intravenous injection of the same dose of epinephrine. Support for claims 165-166 is found on page 46, line 32 to page 47, line 2. Claims 167-168 recite that the average time for epinephrine Tmax in the patient's blood plasma is lower than for non-intravenous injection of the same dose of epinephrine. Support for claims 167 -168 is found on page 47, lines 3-4. Claim 169 recites that the Tmax of epinephrine in a patient's blood plasma is less than about 5 minutes. Support for claim 169 is found on page 49, line 1. Claim 170 recites that the Cmax of epinephrine in a patients blood is about 2-3 times greater than the epinephrine Cmax provided by administration of epinephrine in a liquid-based aerosol. Support for claim 170 is found page 47, lines 10-13.

Appealed claim 172 is an independent claim and is directed to particles for delivery of epinephrine to the respiratory system comprising: (a) about 11 to about 21 weight percent epinephrine bitartrate; (b) about 62 to about 82 weight percent leucine; and (c) about 7 to about 17 weight percent sodium tartrate. This claim is supported on page 6, lines 16-28.

Appealed claim 173 is an independent claim and is directed to methods of treating a patient in need of epinephrine by administering an effective amount of particles to the respiratory system of the patient, the particles comprising: (a) about 11 to about 21 weight percent epinephrine bitartrate; (b) about 62 to about 82 weight percent leucine; and (c) about 7 to about 17 weight percent sodium tartrate. This claim is supported on page 6, lines 16-28.

(6) Grounds of Rejection to be Reviewed on Appeal

- Claims 140-143, 153, and 156-160 are finally rejected under 35 U.S.C. §103(a) as being unpatentable over Tarara (US 2005/0074498) in view of Slutsky (U.S. Pat. No. 6,102,036).
- Claims 161-162 are finally rejected under 35 U.S.C. §103(a) as being unpatentable over Tarara et al. (US 2005/0074498) in view of Slutsky (U.S. Pat. No. 6,102,036) as applied to claims 140-143, 153, and 156-160 and further in view of the 56th edition (2002) of the Physician's Desk Reference (hereinafter the "PDR").
- Claims 140-143, 146-150, 159-160 and 162 are finally rejected under 35 U.S.C. §103(a) over Foster (U.S. 2003/0215512) in view of Tarara (US 2005/0074498) and Slutsky (U.S. Pat. No. 6,102,036).
- Claims 163-170 are finally rejected under 35 U.S.C. §103(a) over Tarara (US 2005/0074498) in view of Slutsky (U.S. Pat. No. 6,102,036) as applied to claims 140-144, 153 and 156-160, and further in view of Warren et al. (*Clin. Pharmacol. Ther*. (1986) **40**(6), 673-678).
- Claims 172 and 173 are finally rejected under 35 U.S.C. §103(a) as being unpatentable over Foster (U.S. 2003/0215512) in view of Tarara (US 2005/0074498) and Slutsky (U.S. Pat. No. 6,102,036) and further in view of Drug Information Handbook ("DIH").

(7) Argument

A. *Claims 140-143, 153, and 156-160 are finally rejected under 35 U.S.C. §103(a) as being unpatentable over Tarara (US 2005/0074498) in view of Slutsky (U.S. Pat. No. 6,102,036).*

The Examiner's lengthy rejection made in the Final Office Action dated December 10, 2008, will not be repeated here for the sake of expediency. In that rejection, the Examiner concludes that it would have been obvious to combine the teachings of Tarara and Slutsky because Tarara teaches powdered formulations for inhalation and Slutsky teaches breath activated inhalers and Slutsky's inhaler would allow one to deliver a large dose in a single breath. The Examiner further asserts that the combination of Tarara's compositions with Slutsky's invented inhaler would reasonably be expected to deliver at least 50 micrograms of epinephrine, because one can modify the dosage of epinephrine present in the inhaler to ensure the delivery of a therapeutically amount of epinephrine and Slutsky's inhaler permits delivery of an entire dose in a single breath. Appellants respectfully disagree.

To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. There must also be a reasonable expectation of success. *See* M.P.E.P. § 2143. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in Appellant's disclosure. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Thus, "particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed inventions, would have selected these components for combination in the manner claimed." *In re Kotzab*, 217 F.3d 1365, 1371 (Fed. Cir. 2000). "The factual inquiry whether to combine references must be thorough and searching. It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with." *In re Sang Su Lee*, 277 F.3d 1338, 1343 (Fed. Cir. 2002) (citations and quotes omitted). Additionally, it is now well-established that "[b]road conclusory statements regarding the teaching of multiple references standing alone are not 'evidence'." *In re Kotzab*, 217 F.3d at 1370. "Th[e] factual question of motivation is material to patentability and [can] not be resolved on subjective belief and unknown authority." *In re Sang Su Lee*, 277 F.3d at 1343-44.

While the Supreme Court in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (U.S. 2007), cautions that the "obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents" (*Id.*, at 1741), the Supreme Court maintains that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently known in the prior art". *Id.*, at 1741. The Supreme Court further notes that "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does". *Id.*, at 1741.

The rejection fails to address each limitation of the claims. In addition to delivering epinephrine via inhalation in a dose of at least 50 micrograms, the claims also require that the epinephrine be in the form of spray-dried particles having specific characteristics (at least 45% of the delivered dose has an FPF of less than 5.6 microns and the particles have a tap density of less than 0.4g/cm^3) which facilitate the highly efficient inhalation of at least 50 micrograms of epinephrine in a single breath activated step. However, the Examiner appears to be asserting that simply because epinephrine is known and is suitable for inhalation, and that an inhaler is known that is capable of delivering large doses in a single breath, the improvements of the present invention are obvious. As Appellants will now show, this is not correct.

Claim 140

1. Tarara

a. Tarara's teachings

Turning to Tarara, powders for administration via an inhaler, such as a dry powder inhaler, meter dose inhaler or nebulizer, are disclosed. Abstract. The powders preferably have a bulk density of less than about 0.5 g/cm^3. Para. [0016]. Tap density is not disclosed. The spray dried powders can incorporate a large number of drugs, one of which is said to be epinephrine (adrenaline). Para. [0070]. When a DPI is use, it is said that the DPI can include unit doses ranging from 5 to 15 mg, corresponding to 25 to 500 mcg or the DPI can be a bulk reservoir system. Para. [0132]. The powders are said to have a fine

particle fraction of at least about 20% (or more) as measured in a specified reference which has not been made of record. Para. [0127]. In the working examples, the powders were "assessed" in accordance with this reference using 10-20 actuations. Para. [0295]. Example XX, which will be discussed in more detail below, exemplifies testing a 300 mcg. Albuterol powder in a DPI. The DPI (stated only to be proprietary) was actuated with pressurized propellant (HFA 134a) ten times (not one time, see the rejected claim 1), resulting in a total FPF of 87% and a "FPD" of 100 mcg/actuation (note the math does not balance). See also Fig. 5. The same powder appears to have been used in Example XXII. Again, 10 actuations were discharged before the FPF was measured. In this example, an inspiratory flow rate of 60 L/min was selected, but the volume of air used or length of each actuation step is not disclosed.

b. Tarara teaches the need for ten to twenty actuations for success, not high FPFs in a single breath

The Examiner infers that Tarara teaches all of the limitations of the claims with respect to the epinephrine powder and its efficiency in delivery. It is Appellants' opinion that the Examiner has made numerous technical errors and incorrect assumptions with regard to the disclosures made in this reference. The Examiner has provided no basis for concluding that Tarara provides a generic teaching that a unit dose container in a DPI which may contain from 5 to 15 mg teaches the desirability and means to deliver at least 50 micrograms of epinephrine (or any other drug) to a patient in need thereof in a *single breath-activated step* at the stated *fine particle fraction less than 5.6 microns*. The Examiner assumes on page 5 of the Final Office Action that a drug loading ranging from 25 to 500 micrograms per dose *must* be delivered in a single actuation with a breath activated inhaler. This is not necessarily true, is not supported by the evidence on this record and is not a logical extension of the reference. The actual dose per actuation (as compared to breath) will depend upon a variety of factors such as the amounts of active agent and the excipients, the product morphology, and the inhaler used. The FPFs described in the reference are the result of *ten* actuations to achieve a single dose, not ***one*** actuation (the specification used a two second actuation to measure FPF; page 62, line 3)!

c. The math in the examples does not add up

The Examiner's characterization of the examples in Tarara are also inaccurate. In Example XXI, for example, Tarara states that the beclomethasone diproprionate (BDP) powder dose delivered to the relevant stages of the cascade impactor is "77 micrograms per actuation". See, Para. [0318] of Tarara. However, in Para. [0315], Tarara states that there were *twenty* actuations. Thus if 300 micrograms of spray dried microspheres were loaded into the inhalation device as stated by Tarara in Para. [0314], it is not possible that the delivered dose was 77 micrograms per actuation as 77 micrograms per actuation multiplied by 20 actuations would far exceed the total number of micrograms of spray-dried powder initially loaded into the inhaler for delivery. Likewise, if 100% of the drug was delivered over 20 actuations, the average amount of drug per actuation could not exceed 50 micrograms. Further, even if 77 (or 100) micrograms of drug were delivered in a single actuation out of the 300 micrograms loaded into the inhaler, an FPF of at least 45% for that actuation was not achieved.

The same problem exists in Example XX which is the source of the data of Figure 5 relied upon by the Examiner in the Final Office Action to show that the distribution of an exemplary particulate composition in an Anderson cascade impactor as delivered by DPI or MDI. According to Figure 5 and Example XX, an MDI delivered an FPD of 77 micrograms at an FPF of 77% and the DPI delivered an FPD of 100 micrograms at an FPF of 87%. However upon inspection of Para. [0307] of Example 20, it states that approximately 300 mcg (micrograms) of spray dried microspheres were loaded into a proprietary DPI inhalation device and that ten actuations were discharged from the device into the impactor. Thus if the FPD according to Figure 5 for the DPI was 100 micrograms and the device was actuated 10 times, the FPD per actuation should have been far less than 100 micrograms or 1000 micrograms should have been loaded into the DPI. The total amount loaded into the MDI as described in Para. [0309] is not given, therefore it is not possible to determine if an FPD for the MDI of 77 micrograms per actuation is accurate.

d. The Examiner erroneously believes that it is appropriate to ignore the data

The Examiner dismisses these facts, stating on page 8 of the Final Office Action dated December 10, 2008, that "Tarara clearly teaches the FPF required by Appellants

claims." Clearly, something is wrong with the data provided in Tarara's examples (and not just in Example XXI as asserted by the Examiner in the Final Office Action) *on its face* for the foregoing reasons. Because the generic teachings are to be understood in the context of the experimental results, one cannot simply ignore the *facts,* and blindly refer only to the generic teachings and make assumptions bridging the missing gaps (e.g., how many actuations does one need to cause before one achieves the disclosed FPFs and FPDs).[2] The Examiner's recitation of Para. [0127] of Tarara makes exceedingly clear that the Examiner cannot read the generic disclosure separately from the Examples because the first sentence states ***"[a]s will be shown subsequently in the Examples***...."

It is impossible to tell from the data presented in Tarara whether at least 50 micrograms of BDP, or albuterol sulfate or any other drug listed in Tarara, can be delivered at the presently claimed FPF in a single, breath-activated step. It is important to keep in mind that present claim 140 doesn't *only* require that the dose be 50 micrograms, or doesn't *only* require that the FPF of a dose be at least 45% or doesn't *only* require delivery of a epinephrine in a single breath activate step. It is the combination of these very important features that provides the sought after improvement defined by the claims. Therefore, in the absence of an accurate calculation provided by Tarara it is clear that Tarara does not teach or suggest most of the features of the presently claimed invention.

e. The math in the specification also does not add up.

The Examiner also relies upon Para. [0132] of Tarara for teaching drug loading and dose. However, like Examples XX and XXI, the numbers in the referenced paragraphs do not **work**. The inhaler is said to be loaded with 5 to 15 mg of product, which "corresponds to a drug loading ... of 25 to 500 μg per dose." That paragraph also states that unit dose DPIs have physical limitations on dose. The preferred products possess at least 50%

[2] It should be noted that Appellants first presented the above technical discussion regarding the bald discrepancies associated with Tarara's data for the Examiner's consideration in Appellants' Response dated July 20, 2006. Appellants have reiterated the same or similar discussion regarding the discrepancies of Tarara's data in every Response or Appeal Brief filed (a total of 6 papers filed by Appellants not including the present Appeal Brief). The Examiner has not once provided any rebuttal or support that refutes Applicant's discussion of Tarara's data. The Examiner simply continues to state that Tarara's FPF fall within the present claims and maintains that Appellants' arguments are unpersuasive because only Example XXI is incorrect. This is not sufficient to overcome what appear to be *numerous* inconsistencies *on the face* of the Tarara reference.

weight active agent. Para. [0068]. Thus, in a 15 mg product, *at least* 7.5 mg is active agent in a *preferred* embodiment. The smallest preferred dose is 2.5 mg. If one assumes the *maximum* 500 μg dose is achieved with the *lowest* value of the preferred range (2.5 mg drug) and the word "dose" refers to the amount of drug delivered (as assumed by the Examiner, irrespective of the number of actuations required to deliver the drug) then the respirable portion (e.g, fine particle fraction of the emitted dose) of the product (500 μg dose out of 2.5 or 7.5 mg drug that is deliverable to the patient) must be *no more* than about 20% or 7%, respectively, far ***less*** than the present claim which requires a fine particle fraction of at least 45%. If one instead assumes the 500 μg to be the amount of active agent in the inhaler of the 15 mg of product (rather than the delivered dose), the drug load is only about 3.3%, well *below* the preferred ranges in Para. [0068]. In this interpretation of the teachings, the *highest* drug load taught is 10% (500 μg of 5 mg), again *far below* the most preferred ranges. The fact that the math simply does not balance and is internally consistent cuts against any assumption the Examiner can make with respect to what the reference teaches the person of ordinary skill in the art. Why should the Examiner assume that his selected passages are the ones the skilled artisan would select and that the remaining, inconsistent passages would be those that are to be ignored? Indeed, it is believed that the person of ordinary skill in the art would conclude that the specification and exemplification were not written with care and would approach all its teachings with doubt. Given that the Examiner is not a person of skill in the art, he cannot make these assumptions.

f. One cannot ignore the problems in the reference and select only the passages one wishes to rely upon

It is axiomatic that one must read the reference teachings as whole. It is true that the patent specification teaches a large number of ranges (drug load, fine particle fraction, amount of drug actuated, dose delivered, inhaler selection and operation) which values or parameters can be identified and individually selected to theoretically achieve the claimed combination (always ignoring, however, the requirement that the actuation be in a single breath). However, as established by comparing a very few of the ranges above, these numbers are internally inconsistent and appear to be arbitrary. It is respectfully asserted

that such teachings of what is "preferred" cannot be said to provide any meaningful guidance that renders the claimed selection obvious. Tarara simply does not even teach highly efficient administration of drugs (products having an FPF of at least 45%) to normal healthy patients in a single breath, much less the administration of epinephrine at an FPF of 45% in a single breath to patients who are in need of epinephrine which is generally a population of patients that are in acute need of relief, such as patients suffering from anaphylaxis.

g. No reason to select epinephrine and assume efficient delivery in a single breath actuated inhaler

The Examiner has also not provided any discussion as to why one skilled in the art would choose epinephrine (mentioned in a long list in Tarara) to deliver by inhalation. Without the benefit of hindsight in view of the present invention, one skilled in the art would not be motivated to rely on a breath-actuated dry powder inhaler to deliver a life saving drug in a crisis situation that may involve difficulty in breathing. At best, if one were to attempt delivering epinephrine to a patient according to the teachings of Tarara, one would select the preferred MDIs or a propellant actuated bulk reservoir DPIs. Even in this embodiment, one would not necessarily expect that the efficiency of delivery to be so high. Yet, as disclosed in the present examples page 92, lines 8-16, T_{max} and C_{max} were *superior* to injection using the EPIPEN® and standard IM injection.

2. Slutsky

Slutsky teaches a breath activated inhaler modified to improve the delivery of nicotine and similar drugs while reducing throat irritation.

Turning now to the Examiner's characterization of Slutsky, the Examiner states that Slutsky teaches a breath activated inhaler, which may contain a single dose of a powdered medicament, which is intended to be inhaled by the patient in a single breath. The Examiner further states that Slutsky teaches an alternative breath activated inhaler capable of delivering a large dose of powdered medicament in a single breath. This is not disputed. In fact, single-breath activated inhalation devices were disclosed by Appellants on page 57, lines 14-21 of the present specification. Slutsky also makes reference to those

same prior art inhalers at column 6, lines 16-27, and discloses that the inhaler invented by Slutsky is in fact a modified form of these standard inhalers (see column 6, lines 28-60, and column 7 lines 20-34 describing the modification to the known inhalers of the prior art).

It should be noted, however, that Slutsky's modifications to the inhaler render the single breath-activated inhaler *less suitable* for the delivery of epinephrine to a patient in need of epinephrine and who may be having difficulty breathing. Slutsky's modifications to the breath activated inhalers of the prior art are intended to *restrict* the cross-sectional area of the air conduit so as to *reduce* the flow rate of air (column 7 lines 14-34). In one embodiment Slutsky discloses *increasing the resistance* of the inhaler to *slow the administration* of nicotine and thereby provide greater comfort to the patient (column 3, lines 59-61). In another embodiment Slutsky discloses an air by-pass means intended to *reduce the concentration* of the medicament in the air which inhaled by the patient to avoid irritation to the patient's throat (column 4, lines 50-57 and column 12, lines 47-63). In another embodiment, Slutsky discloses that one treatment may consist of *multiple inhalations* of a smaller dose over a period of time (column 7, lines 4-14 and column 12, lines 47-63). The assumption by Slutsky is that the prior art inhalers have low resistance because they are being used by a person having difficulty breathing, but for patients requiring nicotine who are not in respiratory distress, the absence of resistance by a healthy breath could cause impaction of nicotine at the back of the throat (Column 7, lines 14-23). Thus Slutsky modifies the inhaler to restrict the air flow, reduce drug concentration and increase resistance whether or not a single breath or multiple breaths are used by the patient. Slutsky's need to provide a large dose of a specific drug, nicotine, while preventing irritation does not require highly efficient delivery of a drug having specific characteristics in order to achieve such highly efficient delivery.

3. No motivation to combine in light of the reference teachings

One skilled in the art would not be motivated to combine Slutsky's inhaler which is intended to restrict the flow rate of large doses of nicotine to a healthy breather with a therapeutic such as epinephrine for delivery to a person who may be having difficulty breathing and wherein relief in as little as a single breath is essential. When taken as a

whole, Slutsky simply does not provide teachings that the skilled practitioner would turn to in the context of the present invention or use in combination with Tarara to arrive at the presently claimed invention.

4. The Examiner's allegation that Appellants are arguing limitations not found in the claims misses the point

In the Final Office Action dated December 10, 2008, the Examiner has argued that Appellants are arguing features not present in the claims (e.g. that patients in need of epinephrine may have difficulty breathing). In the Office Action dated August 27, 2008, the Examiner pointed out that epinephrine has been used to treat glaucoma, which is not a situation in which a patient has difficulty breathing. The Examiner uses this information to support his position that the inhaler of Slutsky which is modified to restrict the flow rate of therapeutic delivered to the patient by inhalation would not teach away from the presently claimed invention in the absence of the present claim excluding glaucoma. The Examiner suggests amending the claims to exclude glaucoma.

The Examiner is missing the point entirely with regard to fairly evaluating what the Slutsky reference as a whole teaches. In accordance with MPEP 2141.02, "[a] prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)". A skilled person who is seeking highly efficient delivery of epinephrine *by inhalation* is not concerned with treating glaucoma (a condition that is well understood in the art to be *treated by topical eye drop administration only* of epinephrine and not by inhalation of epinephrine) but is concerned with delivering epinephrine in those instances which require highly efficient delivery of the drug. Such circumstances are those outlined in the background section of the present application and generally define a patient who has urgent need of the epinephrine. Thus, the necessary features of highly efficient delivery *are already present in the claims* (e.g. drug dose in combination with particle morphology and FPF) and it is clear that neither Slutsky nor Tarara when taken alone or in combination, teach, suggest or disclose these critical features.

In the Final Office Action dated December 10, 2008, the Examiner also stated that Appellants misunderstood that Slutsky is relied upon by the Examiner for its teaching of administration in a single breath activated step and not for a teaching of fine particle fraction. Appellants did not misunderstand. Appellants were merely pointing out that the present claim requires not only administration in a single breath activated step, but also requires that the drug being administered in that single breath-activated step meet the other features of claim 140 including the FPF and that neither Slutsky or Tarara disclose this critical feature, among others, that are presently claimed. It appears that it is undisputed that Slutsky is silent with regard to FPF. What is disputed is whether Tarara discloses the presently claimed dose having the presently claimed FPF. Throughout the prosecution of this application, Appellants have provided ample technical discussion regarding the lack of disclosure of FPF and dosage and the inconsistencies in Tarara data on its face. The Examiner has never rebutted Appellants' findings.

5. Summary

The features of highly efficient delivery i.e. the criticality of the combination of fine particle fraction and tap density to deliver a high dose of the epinephrine via the epinephrine-containing particles was not appreciated at the time of the invention and can only be arrived at by using information that was *not available* to the skilled practitioner at the time of the present invention, such as by improper hindsight reconstruction based on the data and information of the present application. To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. The Examiner has failed to provide a reference which teaches a means of modifying Tarara and/or Slutsky to achieve fine particle fraction necessary to achieve the highly efficient delivery of epinephrine at the necessary effective dose as is presently claimed. Clearly, the combination of Tarara and Slutsky do not teach or suggest critical features of the present claims.

The Examiner has failed to show that the claims are obvious in view of the cited combination of references. Reversal of the rejection under this section is respectfully requested.

Claims 142 and 143

Tarara does not teach the selection of 1 to 45% and 1 to 30% (respectively) by weight of epinephrine. As discussed above, the preferred powder fill (5 to 15 mg) and drug loading (25 to 500 μg per dose) does not result in the percentages disclosed here. There is simply no guidance whatsoever to make any specific dosing selections for any specific drug, much less epinephrine. An effective dose requires the careful selection of the powder fill, drug amounts and an understanding of the efficiency at which the dose will be delivered. These teachings with respect to epinephrine are absent. Thus, these claims are independently non-obvious over the prior art.

Claims 153

Tarara does not teach the selection of a powder that contains about 250 micrograms to about 5 milligrams of epinephrine. As discussed above, the preferred powder fill (5 to 15 mg) and drug loading (25 to 500 μg per dose) does not align with the totality of the teachings in the reference. There is simply no guidance whatsoever to make any specific dosing selections for any specific drug, much less epinephrine. An effective dose requires the careful selection of the powder fill, drug amounts and an understanding of the efficiency at which the dose will be delivered. These teachings with respect to epinephrine are absent. Thus, this claim is independently non-obvious over the prior art.

Claims 156-160

Tarara does not teach the selection of a powder that is designed to deliver epinephrine to the upper airways (Claim 158), alveoli (Claim 157) or both (Claim 156) and the corresponding ability to target systemic (Claim 159) or local (Claim 160) activity. In fact, the reference is completely silent as to the site of delivery for this drug. Thus, these claims are independently non-obvious over the prior art.

B. *Claims 161-162 are finally rejected under 35 U.S.C. §103(a) as being unpatentable over Tarara et al. (US 2005/0074498) in view of Slutsky (U.S. Pat. No. 6,102,036) as applied to claims 140-143, 153, and 156-160 and further in view of the 56th edition (2002) of the Physician's Desk Reference (hereinafter the "PDR").*

Claims 161 and 162 depend from Claim 140 and further define the patient to be treated (i.e., a patient suffering from anaphylaxis (Claim 161) and a patient suffering bronchoconstriction, bronchospasm, airway constriction, or edema (Claim 162)). The combination of Tarara and Slutsky are relied upon by the Examiner as above and for the reasons discussed above. The PDR is relied upon to show that epinephrine is known to treat these diseases. For all the reasons set forth above, this rejection must also fall.

Further, while it is not disputed that the PDR establishes that epinephrine is known to treat these diseases, it is not conceded that it would be obvious to treat these kinds of diseases by pulmonary delivery of the *specific* product that is described in Claim 140 resulting in *unexpectedly improved* treatment methods for the claimed conditions. Given the high efficiencies in delivery and the large cloud that will result from the actuation of a highly efficient and large dose, it is not at all obvious to treat a patient suffering from anaphylaxis (Claim 161) and a patient suffering bronchoconstriction, bronchospasm, airway constriction, or edema (Claim 162). The fact that the PDR suggests that the drug is known to be administered for a given disease does not necessarily support a conclusion that any and all modes of administration and formulations of that drug would be obvious. If this were true, improved methods of delivery and associated formulations would be *per se* unpatentable and this is not the current state of patent law. Appellants are claiming an improved and highly efficient method for administering epinephrine. As discussed above, the combination of Tarara and Slutsky do not make the present invention obvious. And, for the reasons discussed above, Slutsky teaches away from methods of treating a patient in anaphylaxis (Claim 161) and a patient suffering bronchoconstriction, bronchospasm, airway constriction, or edema (Claim 162). The citation of the PDR adds nothing to this combination other than what is known in the art about indications for epinephrine. Claims 161 and 162 are not obvious in view of the cited combination of references. Withdrawal of the rejection under this section is respectfully requested.

C. *Claims 140-143, 146-150, 159-160 and 162 are finally rejected under 35 U.S.C. §103(a) over Foster (U.S. 2003/0215512) in view of Tarara (US 2005/0074498) and Slutsky (U.S. Pat. No. 6,102,036).*

The Examiner states that Foster lacks the teaching of compositions having a tap density of less than 0.4 g/cm^3 which is cured by the teachings of Tarara. The Examiner also states that Foster lacks the teaching of administration in a single breath activated step which is cured by Slutsky. The Examiner further asserts that one would have motivated to combine Foster and Tarara because Tarara's compositions provide aerodynamically light particles suitable for inhalation. The Examiner also asserts that the skilled person who is aware of Slutsky would be motivated to use Slutsky's breath activated inhaler to improve patient compliance and delivery active agent in the fewest number of administration. The Examiner concludes that one would expect success upon combination as both Tarara and Foster teach epinephrine for pulmonary administration. Appellants respectfully disagree.

As above, the Examiner has ignored several claim limitations and has seriously oversimplified the many variables that go into making a particle composition suitable for inhalation and this highlights the Examiner's misunderstanding of the presently claimed invention.

Claim 140

1. Foster teachings

Foster teaches that one can improve solid state stability of drugs, such as proteins, over time. The solution to that problem is to form the protein in the presence of a glassy matrix. The products formed by spray drying the matrix and drug are not perforated spheres. Figure 6.

2. Tarara and Foster cannot be combined

Tarara discloses hollow and/or perforated microstructures of low density. See Para. [0015]. Tarara discloses the many advantages that this specific morphology provides to improve particle flowability and other characteristics. Paras. [0015] and [0019]. Thus it is clear that this particle morphology is essential to achieve the results disclosed in Tarara. To form these perforated spheres, Tarara spray dries a phospholipid with the drug. In contrast, Foster is concerned with creating a glassy matrix with the drug and adds excipients such as sugars. Para. [0071]. Phospholipids are not described and do not appear to be suitable for producing a glassy matrix.

Furthermore, the particles of Foster are *solid* [0044] (and, therefore, dense), spheroidal or "raisin-like" with surface convolutions [0051], not hollow and perforated. That is, the density of a solid particle such as that described in Foster will be understood in the art to be around 1 g/cm^3. This is also supported in Foster in Para. [0051] wherein the aerodynamic diameter ranges (MMAD) and the mass median diameter ranges (MMD) are about the same.[3] Thus the solid particles of Foster having a tap density of about 1 g/cm^3 would need to be abandoned for the hollow particles of Tarara to achieve the tap density described there. The morphology of Foster's particle compositions also appears to be important to the results obtained therein as is described in [1149], [0050] and [0051].

Thus, while both Tarara and Foster provide compositions "suitable for inhalation" as asserted by the Examiner, the compositions disclosed in each reference are no more alike then an antibody composition and a small molecule composition that may both be "suitable for injection". The Examiner has not articulated *how* one would combine the teachings of Foster and Tarara, retaining the important features of each, and thereby provide a composition suitable for inhalation with the Slutsky inhaler. Indeed it would be necessary to forfeit the very important features of one or the other of the Tarara and Foster compositions in order to make such a combination. Such a change is not supported by the disclosure of either Tarara or Foster.

Clearly, the problems faced by Foster and Tarara differ. The solutions differ and both rely on the selection of distinct excipients. There is no reason to believe that one, starting from Foster, would choose to add a phospholipid to its product and reduce the glassy matrix formed thereby. There is no reason to believe that one, starting from Tarara, would be motivated to add a glassy matrix and reduce the perforated, hollow microstructure formed thereby.

As set forth in MPEP 2143.01, "[i]f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)". In this situation, the addition of the phospholipid to Foster, while it *may* facilitate the production of a hollow sphere, would reduce the glassy

[3] Using the Gonda formula on page 30 line, 27, of the present application, the theoretical calculation for density confirms that the Foster particles have a density of around 1 g/cm^3.

matrix and, thereby, reduce protein stability. Because that would modify Foster's intended purpose, there can be no motivation to combine these references.

The Examiner asserts (see Final Office Action dated December 10, 2008 at page 16) that Appellants have "speculated" that the combination of the teachings of Foster and Tarara would yield particles exhibiting incompatible morphologies for the inhalation administration practiced in each respective reference. The Examiner asserts that in the absence of objective evidence to the contrary, "Attorney speculative arguments" are not found persuasive. Appellants respectfully disagree.

There is nothing speculative about the *actual disclosure* of Tarara at Para. [0019] that states:

> it will be appreciated that the disclosed perforated microstructures reduce attractive molecular forces such as van der Waals forces which dominate prior art powdered preparations. That is, unlike prior art preparations comprising *relatively dense*, *solid particles* or nonporous particles (e.g. micronized) the powdered compositions of the present invention exhibit increased flowability, and dispersability due to the lower shear forces. In part, this reduction in cohesive forces is a result of the novel production methods used to provide the desired powders [empasis added].

Compare to the *actual disclosure* of Foster at Para. [0044] wherein the particles of the powders described therein are *solid*. In the above passage, Tarara specifically states that the particles described therein overcome the drawbacks of *prior art solid particles* such as those described in Foster. There is no speculation involved in interpreting Tarara and Foster, just a critical reading of the information disclosed in both references. If the Examiner believes that despite the critical differences in the particle morphology between the two references, that they may be combined in the manner the Examiner has set forth, it is up to the Examiner to provide objective evidence to support his point. Otherwise, the references *on their face* provide sufficient evidence that they are incompatible and as such, there is no motivation for such a combination.

3. Foster also does not teach the FPF limitation

Furthermore, Foster does not disclose the presently claimed FPF of the particles as asserted by the Examiner. The data disclosed in Tables [0232] and [0234] of Foster are not generated using a breath activated device. As defined in the application, the term "single, breath-actuated step" means that the particles are dispersed and inhaled in one step wherein the energy for the dispersion is provided solely by the patient. See, page 57, lines 6-24 of the present specification. Foster instead uses a particle dispersion device which first aerosolizes the powder (without breath activation) to form a standing cloud of particles which are then delivered to the aerosol chamber. Para. [0103]. However, whether or not this measurement mimics a single breath is not stated and this would not be assumed. Thus, the claim limitation is missing.

4. As above, Slutsky does not bridge the gap

The Examiner states that the skilled artisan cognizant of the teachings of Slutsky would be motivated to utilize Slutsky's inhaler to deliver a formulation in the fewest number of administrations. This is a mischaracterization of Slutsky. When taken as a whole Slutsky is clearly not teaching the delivery of a formulation in the fewest number of administrations. Slutsky is faced with the problem of needing to deliver a drug by inhalation which requires a very high dose (nicotine) in a manner that does not irritate the patient. The Examiner relies on column 4, lines 47-49 wherein it is stated that the invention *may* contain a single dose of medicament which is intended to be inhaled by the patient in a single breath. However, that sentence is immediately followed by the sentence stating that if the dose required is sufficiently great an air by pass means is provided to reduce the concentration of the medicament in the air which is inhaled by the patient. See also column 12, lines 47-63 discussing that while a large dose may be inhaled, it *may* not be possible for the patient to inhale such a large dose without discomfort and multiple inhalers or dilute air are required to resolve the problem. Slutsky teaches the need to avoid irritation and control delivery by using an appropriate number of breaths, which may be one in some instances. Slustky simply does not teach that one breath is best.

In the Final Office Action dated December 10, 2008, the Examiner states that one would assume that the FPF results of Foster's compositions when administered from a

breath-actuated device would necessarily meet the presently claimed FPF and the burden is on the Appellants to prove the contrary. Appellants disagree. First, the burden of proof is upon the Examiner, not the Appellants.

Further, the record establishes that bulk reservoir DPIs behave differently from unit dosage DPIs (see Tarara Examples XX+). It is common sense that the amount of many powders dispersed by external energy will disperse differently from that powder dispersed by an individual as the energies used to disperse the products will be different. The dispersibility of powders is well established as being variable. The claims require the administration of a highly dispersible powder, as measured by its ability to disperse efficiently in a breath activated inhaler. The specification teaches how to make such powders. There is no reason to believe that any powder existing in the prior art will also inherently possess that property. If the Appellants carried any burden, it has been satisfied.

Each feature of the present claims is integral to the invention including the characteristics of the particles such as the claimed FPF which renders them highly disbursable and that are to be administered in a *single, breath-activated step*. Appellants clearly define what is meant by the term "single breath-activated step" on page 57, lines 10-12 of the specification. As defined therein, a single breath activated step relies upon the energy of the subject's inhalation. Foster instead uses particle dispersion device which first aerosolizes the powder (without breath activation) to form a standing cloud of particles which are then delivered to the aerosol chamber (Para. [0095] of Foster) using a device having an airflow rate of 30L/min for 2.5 seconds. Thus, the presently claimed invention is clearly different from that of Foster. If it is the Examiner's position that these different means for delivering and measuring particles are indeed the same and result in the same FPF, it is the Examiner's burden to provide the object evidence to prove his point. Such evidence has not been provided.

The Examiner has failed to substantiate that the presently claimed invention is *prima facie* obvious in view of the cited combination of references for all of the reasons described above. Reversal of the rejection under this section is respectfully requested.

Claims 142 and 143

Foster does not teach the selection of 1 to 45% and 1 to 30% (respectively) by weight of epinephrine. There is simply no guidance whatsoever to make any specific dosing selections for epinephrine. An effective dose requires the careful selection of the powder fill, drug amounts and an understanding of the efficiency at which the dose will be delivered. These teachings with respect to epinephrine are absent. Thus, these claims are independently non-obvious over the prior art.

Claims 146-150

Claims 146-147 and 149 require that the particles and/or epinephrine and/or excipients are amorphous while Claim 148 and 150 requires the particles and/or excipient to be crystalline. Foster teaches adding a glass former as an improvement over an amorphous or crystalline matrix. Para. [0050]. Thus the reference teaches away from the claimed limitations and these claims are independently non-obvious over the prior art.

D. Claims 163-170 are finally rejected under 35 U.S.C. §103(a) over Tarara (US 2005/0074498) in view of Slutsky (U.S. Pat. No. 6,102,036) as applied to claims 140-144, 153 and 156-160, and further in view of Warren et al. (*Clin. Pharmacol. Ther.* (1986) **40**(6), 673-678).

The Examiner relies on Tarara and Slutsky as discussed above and states that, with respect to these claims, Tarara lacks the express teaching of Cmax and Tmax of different administration routes. The Examiner relies upon Warren to show that inhalation of 30 puffs (i.e., not in a single breath) of adrenaline from a pressurized aerosol (not a breath actuated dry powder inhaler) are indicative of what one would expect upon inhalation of Tarara's formulations. The Examiner asserts that based on Warren's data, one would have been motivated to administer epinephrine to a patient and would have had a reasonable expectation that the such administration would result in maximal adrenaline blood serum levels in a shorter period of time when compared administration by injection. Appellants respectfully disagree.

Warren does not suggest or disclose that it would be obvious to administer epinephrine by a breath actuated dry powder inhaler. The inhaler of Warren relies upon

the external energy of a propellant to disperse the drug and then a large number of breaths (30 puffs) to deliver the drug. In addition, claims 163-170 are dependent from claim 140 and include all the features of claim 140. For all the reasons discussed earlier with regard to the combination of Tarara and Slutsky which shall not be repeated here for the sake of expediency, claim 140 is not obvious in view of Tarara and Slutsky. Warren, as the *tertiary* reference, provides no substantive teachings that a highly efficient dose of epinephrine can be achieved in a single breath actuated administration from a dry powder inhaler.

Claims 163-166

Warren compares 15 inhalations of 160 micrograms/puff followed by 30 inhalations of 160 micrograms/puff with a 300 microgram injection. The percentage of the aerosol inhaled was estimated at 10 to 15%. Thus, the total doses appear to be different. The Cmax and Tmax were compared. The coefficients for variation, recited in Claims 163-166, do not appear to have been determined. Thus, Warren's relevance in satisfying the limitations of Claims 163-166 is not clear.

Claims 167-169

Warren compares 15 inhalations of 160 micrograms/puff followed by 30 inhalations of 160 micrograms/puff with a 300 microgram injection. The percentage of the aerosol inhaled was estimated at 10 to 15%. Thus, the total doses appear to be different. The Cmax and Tmax were compared. While the Tmax for inhalation was shorter than that for injection, the doses were not the same. Thus, the limitations in these claims has not been taught.

Claim 170

Warren compares 15 inhalations of 160 micrograms/puff followed by 30 inhalations of 160 micrograms/puff with a 300 microgram injection. The percentage of the aerosol inhaled was estimated at 10 to 15%. Thus, the total doses appear to be different. The Cmax and Tmax were compared. While the Cmax for inhalation was disclosed with a

different dose by injection, the claim limitation, which defines the efficacy of a dry powder is compared to an aqueous aerosol is not taught.

Summary

Warren is a reference which merely describes that which is already known in the art with regard to the comparative effectiveness of epinephrine administered by inhalation and epinephrine administered by injection and does not cure the defects of the combination of Tarara and Slutsky. Warren does not provide any additional motivation or teachings over Tarara and Slutsky which are alleged by the Examiner to already "teach" administration of epinephrine by inhalation to patients in need thereof. Even if Warren were to give the skilled practitioner the idea of administering epinephrine by inhalation to a patient with the expectation that such administration would be effective on its own, the Examiner still hasn't provided any reasoning or reference that would lead the skilled practitioner to prepare an improved and highly efficient delivery (claimed FPF and dosage in a single breath activated step) using a prior art breath activated inhaler including Slutsky's for all of the reasons discussed previously in this Appeal Brief. Appellants do not merely claim the administration of epinephrine by inhalation. Appellants' invention when viewed as a whole is directed to methods of improved, highly efficient delivery of epinephrine which requires that at least 50 micrograms of epinephrine in particulate form be delivered to the patient and that at least 45% of the delivered particles have an FPF of less than 5.6 microns.

None of the references when taken alone or in combination disclose or suggest such highly efficient delivery of epinephrine. Reversal of the rejection under this section is respectfully requested.

E. Claims 172 and 173 are finally rejected under 35 U.S.C. §103(a) as being unpatentable over Foster (U.S. 2003/0215512) in view of Tarara (US 2005/0074498) and Slutsky (U.S. Pat. No. 6,102,036) and further in view of Drug Information Handbook ("DIH").

The Examiner relies on the teachings of Foster, Tarara and Slutsky as above with respect to Claim 140. The Examiner states that the DIH is a standard reference used in the

pharmaceutical art and the two other two prior art references teach pharmaceutical compositions comprising epinephrine. The Examiner asserts that the skilled person would have been motivated to combine the teachings of the DIH with those of Tarara and Foster because DIH discloses that epinephrine is a known active agent and epinephrine bitartrate is a common salt of said active used in commercially available pharmaceutical formulations. The Examiner states that the use of epinephrine bitartrate would have been apparent to a skilled artisan because it is "one of the most common salts of epinephrine employed in pharmaceutical formulations." The Examiner relies upon Foster to teach adding a glass former, such as tartrate, and an additional excipient such as leucine in the formulation. Regarding the amounts of each ingredient, the Examiner asserts that the teaching in Foster of a range of 0.05% to 99.0% active agent makes obvious the selection of 11 to 21% epinephrine bitartrate and, with respect to the remaining excipients, it is a parameter that is routinely optimized. Appellants respectfully disagree.

While both Foster and Tarara mention adrenaline (epinephrine) as part of a long list of actives, the mere fact that both references disclose overlapping lists of active agents for incorporation of particles does not provide the skilled practitioner with an expectation of successfully mixing and matching specific excipients and active agents in specific amounts. Neither reference discloses or suggests the desirability of producing the specific epinephrine formulation of claims172 and 173 nor has the Examiner provided any evidence that would motivate the skilled practitioner to combine the teachings of Foster and Tarara and Slutsky in order to prepare epinephrine containing particles. The Examiner has merely concluded that because both references mention both "particles" and "adrenaline" that they should be combined. This is improper.

The specific formulations are not reasonably taught by Foster or the primary reference, alone or when combined with Tarara and Slutsky and the DIH. Foster teaches a nearly infinite number of possible combinations of a large number of active agents and a large number of excipients. There is no guidance within Foster's broad generic disclosure to couple epinephrine bitartrate, leucine and sodium tartrate in the specific amounts claimed.

The preferred active agents of Foster appear to be proteins, polypeptides and other macromolecules. Although small molecule drugs are also described and may be

"adrenalin," specific salts thereof are not disclosed. It is noted that salts of many drugs are described in the same list. Had Foster intended to teach salts of epinephrine, he would have. With respect to the amount of active agent added, the reference's range of 0.05% to 99.0% by weight of active agent is, essentially meaningless because it spans the entire range of possible amounts. That is, it is difficult to imagine a therapeutically effective product where the amount of active agent is substantially lower than 0.05%. Further, since Foster appears to rely upon the formation of a glassy matrix and since the Examiner has not shown that epinephrine would be expected to be glassy, it is not clear that Foster teaches a 99.0 or 100% epinephrine formulation. In any event, a range of essentially no active agent to essentially all active agents is not a meaningful teaching of any particular amount of drug to add. The preferred range of between 0.2% and 97% is hardly more meaningful. Para. [0054]. Such a range hardly suggests to the person of skill in the art to select the range between 11 and 21%. The only small molecule working examples carried less than 5% drug. See Example 16.

The excipients of Foster span several columns. The Examiner relies upon the teaching of adding a "glass former" to suggest that sodium tartrate can be added. In fact, the reference suggests that any glass former can be used and, where the drug itself forms a glass, can be omitted altogether. Para. [0064]. Sodium tartrate is one of several glass formers that could be used, in addition to peptides, carbohydrates such as mannitol (when used in combination with, for example, glycine) or lactose, citric acid and sodium citrate. Sodium citrate was the structurally closest glass former actually used. However, it appears that all of the working examples employed large amounts of glass formers, in various combinations. There is no guidance to select between about 7 and 17% of this particular compound. There is no suggestion that this particular combination would be expected to result in a glassy matrix.

Furthermore, the claims require the addition of a large amount of leucine. Leucine is not disclosed as a preferred excipient (or "additive") and there is no guidance in this reference which would suggest that it would be desirable to select leucine and add it in a large quantity. The amount of any one excipient is also not described in a meaningful way to suggest a preferred amount as the teachings are limited to 3% to 99.8% by weight. Para. [0079]. In fact, this passage suggests that such "additives" should be added in an

amount less than 20% w/w. The claims require the leucine to be added in an amount between about 62 and 82% and Appellants have shown the criticality of a high leucine formulation and provided this evidence in their Response dated September 3, 2008. Copending USSN 10/392,333 includes Example 12 on page 77 which discloses data indicating that formulations comprising an active ingredient in combination with a high percentage of leucine as an excipient provides extended release of the active ingredient. Formulation D of Figures 10 and 11 of copending USSN 10/392,333 most closely compares with the presently claimed formula of claims 172 and 173 and exhibits significantly greater broncoprotection through at least 16 hours when compared with the control. Exhibit A. The reference simply provides no motivation to add such a substantial amount of leucine.

Turning to the working examples of the reference for meaningful guidance, 66.2% mannitol, 13.1% sodium citrate and 0.7% citric acid was used with 20% zinc-insulin in Example 1; 18.2% mannitol, 59.1% sodium citrate, 0.1% citric acid and 2.6% glycine was used with 20% zinc-insulin in Example 2; 10.1% mannitol, 27.1% sodium citrate, 0.2% sodium ion and 2.6% glycine was used with 60% zinc-insulin in Example 3; 18.3% mannitol, 19.0% sodium citrate, 0.2% sodium ion and 2.6% glycine was used with 60% zinc-insulin in Example 4; 77.3% sodium citrate, 0.1% citric acid and 2.6% glycine was used with 20% zinc-insulin in Example 5; and so on. Not one example employs an amino acid at high concentrations; not one example employs either leucine or sodium tartrate; not one example employs epinephrine, much less epinephrine bitartrate. A sugar is present in almost every working example. The vast majority of the working examples formulate a protein or peptide. Albuterol sulfate, the only small molecule exemplified, was formulated with 95% or 98% lactose. There is simply no motivation in this exceedingly broad disclosure of a nearly infinite number of possible combinations to select the specific excipients of the claims, in the specific amounts and combine them with epinephrine.

With regard to the addition of Slutsky as a secondary reference, as discussed above, Slutsky provides no more information about the prior art inhalers than is already disclosed in the present specification. Moreover, the modifications to the prior art breath activated inhalers disclosed in Slutsky are intended to restrict air flow and reduce drug

concentration. Clearly the skilled practitioner would not choose an inhaler as provided by Slutsky that would restrict a patient's inhalation of an epinephrine therapeutic.

More is required to support a *prima facie* case of obviousness than the mere fact that the words of the claim can be found within reference and the unsupported assertion that the rest that is missing from the reference is mere routine optimization. See *In re Baird*, 16 F.3d 380, 382; 29 USPQ2d 1550 (CCPA 1979).

In the Final Office Action dated December 10, 2008, the Examiner states that the selection of sodium tartrate in particular is one of only 8 preferred glass formers according to Foster and thus does not occur from a vast list of as alleged by the Appellants in their arguments. The Examiner then asserts that the skilled person would somehow know that it is possible to mix epinephrine bitartrate, sodium tartrate and leucine because all the components are taught by the prior art. If the Examiner is correct and this is the current state of the patent law than the DIH and any reference like it would render every formulation ever conceived obvious. The Examiner's reasoning is clearly faulty.

In the Final Office Action dated December 10, 2008, the Examiner states that Applicants reference to data contained in a copending application USSN 10/392,333 is data that can not be relied upon because it has not been presented in a proper §1.132 declaration and the copending application has not been incorporated by reference. The Examiner is incorrect and his refusal to consider this information is improper. First, there is no rule that requires all evidence to be presented in the form of a §132 declaration. Second, the specification of USSN is not only fully available to the staff of the USPTO but is also a published document published as U.S. Publication Number 20040042970 and the entire prosecution history thereof is also "published". Third, the data contained in the application has been sworn to be accurate by the inventors of that application under 37 C.F.R. §1.163.

The Examiner further argues that formulation D of USSN 10/392,333 is not commensurate with the scope of claims 172 and 173 because it lacks sodium tartrate and epinephrine and has other differences from the presently claimed formulation. The Examiner asserts that due to these differences, one is unable to conclude that any properties observed in formulation D of USSN 10/392,333 are solely due to the presence of 80% leucine. Applicants disagree. The specification of USSN 10/392,333 along with

its file history provides data showing that formulations comprising identical ingredients but in different amounts, one high leucine and the other low leucine, shows the unexpected properties described therein including improved stability and improved bronchoprotection (see the Declaration under §1.132 filed on October 22, 2008 in USSN 10/392,333). Therefore, the advantages of a formulation comprising a high percentage of leucine are not specific to the remaining compositions that make up a particular formulation.

In the Final Office Action dated December 10, 2008, the Examiner further asserts that one of ordinary skill in the art would have been motivated to combine the teachings of Tarara and Foster to obtain superior aerosolizable dry powders. For the reasons discussed above with regard to the obviousness rejection over Tarara in view of Foster, Applicants submit that this incorrect. Applicants previously argued that the combination of the two very different particles having very different particle morphologies (Tarara is hollow and perforated and Foster is solid with a glassy surface) would defeat the function of one or the other particles for their purpose.

The Examiner further argues in the Final Office Action that Foster's teachings do not require that the active agent is a glass former. Rather it is a glass forming excipient that forms the glass matrix in which the active agent is found. The Examiner asserts that it therefore not necessary to show that epinephrine forms a glass because the lack of this showing does not render the teachings of the combined references inoperable. However, Foster discloses in Para. [0049] that "the outer most regions, including the outer surface, of the powder particles are in an amorphous glassy state". In Para. [0050] Foster states that "[t]he composition comprises a pharmaceutically acceptable glassy matrix and at least one pharmacologically active material *within* the amorphous glassy matrix" [emphasis added]. Whether or not the epinephrine itself is in a glassy phase is irrelevant. What is relevant is that the outer surface be in a glassy state and it appears from Foster's examples that more of a compound that is also the glass former is required by Foster in order to form the glassy outer matrix of the particles than is claimed in current claims 172 and 173 which recite ranges as low as 7% sodium tartrate.

For these reasons as well as the other reasons discussed earlier when responding to the combination of Tarara, Foster and Slutsky, claims 172 and 173 are not obvious. The

addition of the DIH to the rejection does not cure the shortcomings of the remaining references. Reversal of the rejection under this section is respectfully requested.

(8) Claims Appendix

See Attached

(9) Evidence Appendix

See Attached

(10) Related Proceedings Appendix

See Attached

The Conclusion

As the Examiner has failed to establish a *prima facie* case of obviousness and the unexpected results achieved by the present invention, Appellants request reversal of the rejections and allowance of the application.

Respectfully submitted,

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8. Claims Appendix

140. (Previously Presented) A method for administering epinephrine to a patient in need of epinephrine, the method comprising:

administering spray-dried particles from a dry powder inhaler to the respiratory system of the patient in a single, breath-activated step, the particles comprising:

(a) epinephrine, or a salt thereof; and

(b) at least one pharmaceutically acceptable excipient;

wherein the particles administered to the patient comprise at least about 50 micrograms of epinephrine, have a tap density of less than 0.4 g/cm^3 and possess a fine particle fraction of less than 5.6 microns of at least about 45 percent.

141. (Previously Presented) The method of Claim 140, wherein the epinephrine, or salt thereof, is present in the particles in an amount ranging from about 1 to about 95 weight percent.

142. (Previously Presented) The method of Claim 141, wherein the epinephrine, or salt thereof, is present in the particles in an amount ranging from about 1 to about 45 weight percent.

143. (Previously Presented) The method of Claim 142, wherein the epinephrine, or salt thereof, is present in the particles in an amount ranging from about 1 to about 30 weight percent.

146. (Previously Presented) The method of Claim 140, wherein the particles are amorphous.

147. (Previously Presented) The method of Claim 140, wherein the epinephrine, or salt thereof, contained in the particles is amorphous.

148. (Previously Presented) The method of Claim 140, wherein the epinephrine, or salt thereof, contained in the particles is crystalline.

149. (Previously Presented) The method of Claim 140, wherein the pharmaceutically acceptable excipient contained in the particles is amorphous.

150. (Previously Presented) The method of Claim 140, wherein the pharmaceutically acceptable excipient contained in the particles is crystalline.

153. (Previously Presented) The method of Claim 140, wherein the particles comprise about 250 micrograms to about 5 milligrams of epinephrine.

156. (Previously Presented) The method of Claim 140, wherein a first portion of the particles is deposited in the airways of the respiratory system and a second portion of the particles is deposited to the alveoli region of the lungs.

157. (Previously Presented) The method of Claim 140, wherein administering an effective amount of particles includes delivering a portion of the particles to the alveoli region of the lungs.

158. (Previously Presented) The method of Claim 140, wherein administering an effective amount of particles includes delivering a portion of the particles to the upper airways.

159. (Previously Presented) The method of Claim 140, wherein the epinephrine is released from the particles and acts systemically.

160. (Previously Presented) The method of Claim 140, wherein the epinephrine is released from the particles and acts locally.

161. (Previously Presented) The method of Claim 140, wherein the patient in need of epinephrine is suffering from anaphylaxis.

162. (Previously Presented) The method of Claim 140, wherein the patient in need of epinephrine exhibits at least one of the conditions selected from the group consisting of bronchoconstriction, bronchospasm, airway constriction, and edema.

163. (Previously Presented) The method of Claim 140, wherein the coefficient of variation for the maximum epinephrine concentration, C_{MAX}, in the patient's blood plasma of a dose of epinephrine is lower than for a non-intravenous injection of the same dose of epinephrine.

164. (Previously Presented) The method of Claim 163, wherein the non-intravenous injection is selected from the group consisting of a subcutaneous injection, an intramuscular injection, and an auto-injection.

165. (Previously Presented) The method of Claim 140, wherein the coefficient of variation for the time for maximum epinephrine concentration, T_{MAX}, in the patient's blood plasma of a dose of epinephrine is lower than for a non-intravenous injection of the same dose of epinephrine.

166. (Previously Presented) The method of Claim 165, wherein the non-intravenous injection is selected from the group consisting of a subcutaneous injection, an intramuscular injection, and an auto-injection.

167. (Previously Presented) The method of Claim 140, wherein the average time for maximum epinephrine concentration, T_{MAX}, in the patient's blood plasma of a dose of epinephrine is lower than for a non-intravenous injection of the same dose of epinephrine.

168. (Previously Presented) The method of Claim 165, wherein the non-intravenous injection is selected from the group consisting of a subcutaneous injection, an intramuscular injection, and an auto-injection.

169. (Previously Presented) The method of Claim 140, wherein the median time to maximum epinephrine concentration, T_{MAX}, in the patient's blood plasma is less than about 5 minutes.

170. (Previously Presented) The method of Claim 140, wherein the resulting epinephrine C_{MAX} in the patient's blood plasma is about 2 to about 3 times greater than epinephrine C_{MAX} in the patient's blood plasma provided by administration of a liquid-based aerosol.

171. (Previously Presented) The method of Claim 140, wherein the epinephrine is released from the particles in a sustained manner.

172. (Previously Presented) Particles for delivery of epinephrine to the respiratory system, the particles comprising:

(a) about 11 to about 21 weight percent epinephrine bitartrate;

(b) about 62 to about 82 weight percent leucine; and

(c) about 7 to about 17 weight percent sodium tartrate.

173. (Previously Presented) A method for treating a patient in need of epinephrine, the method comprising:

administering an effective amount of particles to the respiratory system of a patient using a dry powder inhaler, the particles comprising:

(a) about 11 to about 21 weight percent epinephrine bitartrate;

(b) about 62 to about 82 weight percent leucine; and

(c) about 7 to about 17 weight percent sodium tartrate.

9. Evidence Appendix

Exhibit A. Selected papers from the File History of USSN 10/392,333

10. Related Proceedings Appendix

None